EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	kappaM RIIIk	US-PGPUB; USPAT; DERWENT	ADJ	ON	2006/08/14 11:28
L2	1	kappaM RIIIk	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/08/14 11:30
L3	4	kappaM	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/08/14 11:31
L4	1	kM conotox$	US-PGPUB; USPAT; DERWENT	SAME	ON	2006/08/14 11:31

10/666946
File 5:Biosis Previews(R) 1969-2006/Aug W1
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Set Items Description
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Set	Items	Description
S1	3	KAPPAM(W)CONO?
S2	38	KAPPA(W)CONO?
S3	0	S2 AND ISCHEM?
S4	0	S2 AND REPERFUSION
S5	59	CONOTOXIN AND ISCHEM?
S6	6	CONOTOXIN AND REPERFUSION
S7	43	S5 AND CHANNEL
S8	0	S5 AND (POTASSIUM()CHANNEL)
S9	0	S5 AND SHAKER
S10	2226	CHARYBDOTOXIN
S11	59	S10 AND SHAKER
S12	31	S10 AND ISCHEM?
S13	12	S10 AND REPERFUSION
S14	12	S12 AND S13
S15	31	S12 OR S13
S16	388	E2-E10
S17	1	S5 AND S16
S18	2	S10 AND S16

10 " 9.20.07

? t s1/7/1-3

1/7/1
DIALOG(R)File 5:Biosis Previews(R)

0014982340 BIOSIS NO.: 200400353129
Identification of a mammalian target of KM-conotoxin RIIIK
AUTHOR: Ferber Michael; Al-Sabi Ahmed; Stocker Martin; Olivera Baldomero M; Terlau Heinrich (Reprint)
AUTHOR ADDRESS: AG Mol and Zellulare Neuropharmakol, Max Planck Inst Expt Med, Hermann Rein Str 3, D-37075, Gottingen, Germany**Germany
AUTHOR E-MAIL ADDRESS: hterlau@gwdg.de
JOURNAL: Toxicon 43 (8): p915-921 June 15, 2004 2004
MEDIUM: print
ISSN: 0041-0101
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Despite the great variability of the conus peptides characterized until now only relatively few have been identified that interact with K+ channels. KM-conotoxin RIIIK (kappaM-RIIIK) is a 24 amino acid peptide from Conus radiatus, which is structurally similar to mu-conotoxin GIIIA, a peptide known to block specifically skeletal muscle Na+ channels. Recently, it has been shown that kappaM-RIIIK does not interact with Na+ channels, but inhibits Shaker potassium channels expressed in Xenopus oocytes. It was demonstrated that kappaM-RIIIK binds to the pore region of Shaker channels and a teleost homologue of the Shaker channel TShaI was identified as a high affinity target of the toxin. In contrast the mammalian Shaker-homologues Kv1.1, Kv1.3, Kv1.4 are not affected by the

toxin. In this study the activity of kappaM-RIIIK on other mammalian Kv1 K+ channels expressed in Xenopus oocytes was investigated. We demonstrate that %%%kappaM%%%-%%%conotoxin%%% RIIIK up to 5 muM exhibits no significant effect on Kv1.5 and Kv1.6 mediated currents, but the human Kv1.2 K+ channel is blocked by this peptide. The binding of kappaM-RIIIK to Kv1.2 channels is state dependent with an IC50 for the closed state of about 200 nM and for the open state of about 400 nM at a test potential of 0 mV. %%%kappaM%%%-%%%conotoxin%%% RIIIK is the first conotoxin described to block human Kv1.2 potassium channels. Copyright 2004 Elsevier Ltd. All rights reserved.

1/7/2
DIALOG(R)File 5:Biosis Previews(R)

0014979785 BIOSIS NO.: 200400350574
%%%kappaM%%%-%%%conotoxin%%% RIIIK, structural and functional novelty in a K+ channel antagonist
AUTHOR: Al-Sabi Ahmed; Lennartz Dirk; Ferber Michael; Gulyas Jozsef; Rivier Jean E F; Olivera Baldomero M; Carlomagno Teresa (Reprint); Terlau Heinrich
AUTHOR ADDRESS: Mol and Cellular Neuropharmacol Grp, Max Planck Inst Expt Med, Hermann Rein Str 3, D-37075, Gottingen, Germany**Germany
AUTHOR E-MAIL ADDRESS: taco@nmr.mpibpc.mpg.de; hterlau@gwdg.de
JOURNAL: Biochemistry 43 (27): p8625-8635 July 13, 2004 2004
MEDIUM: print
ISSN: 0006-2960 (ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Venomous organisms have evolved a variety of structurally diverse peptide neurotoxins that target ion channels. Despite the lack of any obvious structural homology, unrelated toxins that interact with voltage-activated K+ channels share a dyad motif composed of a lysine and a hydrophobic amino acid residue, usually a phenylalanine or a tyrosine. %%%kappaM%%%-%%%Conotoxin%%% RIIIK (kappaM-RIIIK), recently characterized from the cone snail Conus radiatus, blocks Shaker and TShal K+ channels. The functional and structural study presented here reveals that %%%kappaM%%%-%%%conotoxin%%% RIIIK blocks voltage-activated K+ channels with a novel pharmacophore that does not comprise a dyad motif. Despite the quite different amino acid sequence and no overlap in the pharmacological activity, we found that the NMR solution structure of kappaM-RIIIK in the C-terminal half is highly similar to that of mu-conotoxin GIIIA, a specific blocker of the skeletal muscle Na+ channel Nav1.4. Alanine substitutions of all non-cysteine residues indicated that four amino acids of kappaM-RIIIK (Leu1, Arg10, Lys18, and Arg19) are key determinants for interaction with K+ channels. Following the hypothesis that Leu1, the major hydrophobic amino acid determinant for binding, serves as the hydrophobic partner of a dyad motif, we investigated the effect of several mutations of Leu1 on the biological function of kappaM-RIIIK. Surprisingly, both the structural and mutational analysis suggested that, uniquely among well-characterized K+ channel-targeted toxins, kappaM-RIIIK blocks voltage-gated K+ channels with a pharmacophore that is not organized around a lysine-hydrophobic amino acid dyad motif.

1/7/3
DIALOG(R)File 5:Biosis Previews(R)

0014168353 BIOSIS NO.: 200300125463
A novel Conus peptide ligand for K+ channels.
AUTHOR: Ferber Michael; Sporning Annett; Jeserich Gunnar; DeLaCruz Richard; Watkins Maren; Olivera Baldomero M (Reprint); Terlau Heinrich
AUTHOR ADDRESS: Dept. of Biology, University of Utah, 257 South 1400 East, Salt Lake City, UT, 84112, USA**USA
AUTHOR E-MAIL ADDRESS: olivera@biology.utah.edu
JOURNAL: Journal of Biological Chemistry 278 (4): p2177-2183 January 24, 2003 2003
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Voltage-gated ion channels determine the membrane excitability of cells. Although many Conus peptides that interact with voltage-gated Na+ and Ca2+ channels have been characterized, relatively few have been identified that interact with K+ channels. We describe a novel Conus peptide that interacts with the Shaker K+ channel, %%%kappaM%%%-%%%conotoxin%%% RIIIK from Conus radiatus. The peptide was chemically synthesized. Although %%%kappaM%%%-%%%conotoxin%%% RIIIK is structurally similar to the mu-conotoxins that are sodium channel blockers, it does not affect any of the sodium channels tested, but blocks Shaker K+ channels. Studies using Shaker K+ channel mutants with single residue substitutions reveal that the peptide interacts with the pore region of the channel. Introduction of a negative charge at residue 427 (K427D) greatly increases the affinity of the toxin, whereas the substitutions at two other residues, Phe425 and Thr449, drastically reduced toxin affinity. Based on the Shaker results, a teleost homolog of the Shaker K+ channel, TSha1 was identified as a %%%kappaM%%%-%%%conotoxin%%% RIIIK target. Binding of %%%kappaM%%%-%%%conotoxin%%% RIIIK is state-dependent, with an IC50 of 20 nM for the closed state and 60 nM at 0 mV for the open state of TSha1 channels.

? t s2/7/1-38

2/7/1
DIALOG(R)File 5:Biosis Previews(R)

0015522677 BIOSIS NO.: 200510217177
Slow inactivation in voltage gated potassium channels is insensitive to the binding of pore occluding peptide toxins
AUTHOR: Oliva Carolina; Gonzalez Vivian; Naranjo David (Reprint)
AUTHOR ADDRESS: Valparaiso Univ, Fac Ciencias, Ctr Neurociencias Valparaiso, Gran Bretana 1111, Valparaiso, Chile**Chile
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JOURNAL: Biophysical Journal 89 (2): p1009-1019 AUG 2005 2005

ISSN: 0006-3495
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Voltage gated potassium channels open and inactivate in response to changes of the voltage across the membrane. After removal of the fast N-type inactivation, voltage gated Shaker K-channels (Shaker-IR) are still able to inactivate through a poorly understood closure of the ion conduction pore. This, usually slower, inactivation shares with binding of pore occluding peptide toxin two important features: i), both are sensitive to the occupancy of the pore by permeant ions or tetraethylammonium, and ii), both are critically affected by point mutations in the external vestibule. Thus, mutual interference between these two processes is expected. To explore the extent of the conformational change involved in Shaker slow inactivation, we estimated the energetic impact of such interference. We used %%%kappa%%% - %%%conotoxin%%%- PVIIA (kappa - PVIIA) and charybdotoxin (CTX) peptides that occlude the pore of Shaker K-channels with a simple 1: 1 stoichiometry and with kinetics 100-fold faster than that of slow inactivation. Because inactivation appears functionally different between outside-out patches and whole oocytes, we also compared the toxin effect on inactivation with these two techniques. Surprisingly, the rate of macroscopic inactivation and the rate of recovery, regardless of the technique used, were toxin insensitive. We also found that the fraction of inactivated channels at equilibrium remained unchanged at saturating kappa - PVIIA. This lack of interference with toxin suggests that during slow inactivation the toxin receptor site remains unaffected, placing a strong geometry-conservative constraint on the possible structural configurations of a slow inactivated K-channel. Such a constraint could be fulfilled by a concerted rotation of the external vestibule.

2/7/2
DIALOG(R)File 5:Biosis Previews(R)

0015277839 BIOSIS NO.: 200500184904
Binding of %%%kappa%%%-%%%conotoxin%%% PVIIA to Shaker K+ channels reveals different K+ and Rb+ occupancies within the ion channel pore
AUTHOR: Boccaccio Anna; Conti Franco; Olivera Baldomer M; Terlau Heinrich (Reprint)
AUTHOR ADDRESS: Mol and Cellular Neuropharmacol Grp, Max Planck Inst Expt Med, Hermann Rein Str 3, D-37075, Gottingen, Germany**Germany
AUTHOR E-MAIL ADDRESS: hterlau@gwdg.de
JOURNAL: Journal of General Physiology 124 (1): p71-81 July 2004 2004
MEDIUM: print
ISSN: 0022-1295 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The x-ray structure of the KcsA channel at different (K+) and (Rb+) provided insight in to how K+ channels might achieve high selectivity and high K+ transit rates and showed marked differences between the occupancies of the two ions within the ion channel pore. In this study, the binding of %%%kappa%%%-%%%conotoxin%%% PVIIA

(kappa-PVIIA) to Shaker K+ channel in the presence of K+ and Rb+ was investigated. It is demonstrated that the complex results obtained were largely rationalized by differences in selectivity filter occupancy of this 6TM channels as predicted from the structural work on KcsA. kappa-PVIIA inhibition of the Shaker K+ channel differs in the closed and open state. When K+ is the only permeant ion, increasing extracellular (K+) decreases kappa-PVIIA affinity for closed channels by decreasing the "on" binding rate, but has no effect on the block of open channels,which is influenced only by the intracellular (K+). In contrast, extracellular (Rb+) affects both closed- and open-channel binding. As extracellular (Rb+) increases, (a) binding to the closed channel is slightly destabilized and acquires faster kinetics, and (b) open channel block is also destabilized and the lowest block seems to occur when the pore is likely filled only by Rb+. These results suggest that the nature of the permeant ions determines both the occupancy and the location of the pore site from which they interact with kappa-PVIIA binding. Thus, our results suggest that the permeant ion(s) within a channel pore can determine its functional and pharmacological properties.

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DIALOG(R)File 5:Biosis Previews(R)

0014805541 BIOSIS NO.: 200400176298
A delta-conotoxin from Conus ermineus venom inhibits inactivation in vertebrate neuronal Na+ channels but not in skeletal and cardiac muscles.
AUTHOR: Barbier Julien; Lamthanh Hung; Le Gall Frederic; Favreau Philippe; Benoit Evelyne; Chen Haijun; Gilles Nicolas; Ilan Nitza; Heinemann Stefan H; Gordon Dalia; Menez Andre; Molgo Jordi (Reprint)
AUTHOR ADDRESS: Laboratoire de Neurobiologie Cellulaire et Moleculaire, UPR 9040, CNRS, 91198, Gif-sur-Yvette Cedex, France**France
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JOURNAL: Journal of Biological Chemistry 279 (6): p4680-4685 February 6, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have isolated delta-conotoxin EVIA (delta-EVIA), a conopeptide in Conus ermineus venom that contains 32 amino acid residues and a six-cysteine/four-loop framework similar to that of previously described omega-, delta-, muO-, and %%%kappa%%%-%%%conotoxins%%%. However, it displays low sequence homology with the latter conotoxins. delta-EVIA inhibits Na+ channel inactivation with unique tissue specificity upon binding to receptor site 6 of neuronal Na+ channels. Using amphibian myelinated axons and spinal neurons, we showed that delta-EVIA increases the duration of action potentials by inhibiting Na+ channel inactivation. delta-EVIA considerably enhanced nerve terminal excitability and synaptic efficacy at the frog neuromuscular junction but did not affect directly elicited muscle action potentials. The neuronally selective property of delta-EVIA was confirmed by showing that a fluorescent derivative of delta-EVIA labeled motor nerve endings but not skeletal muscle fibers. In a heterologous expression system, delta-EVIA inhibited inactivation of rat neuronal Na+ channel subtypes (rNav1.2a, rNav1.3, and rNav1.6) but

did not affect rat skeletal (rNav1.4) and human cardiac muscle (hNav1.5) Na+ channel subtypes. delta-EVIA, in the range of concentrations used, is the first conotoxin found to affect neuronal Na+ channels without acting on Na+ channels of skeletal and cardiac muscle. Therefore, it is a unique tool for discriminating voltage-sensitive Na+ channel subtypes and for studying the distribution and modulation mechanisms of neuronal Na+ channels, and it may serve as a lead to design new drugs adapted to treat diseases characterized by defective nerve conduction.

2/7/4
DIALOG(R)File 5:Biosis Previews(R)

0014784063 BIOSIS NO.: 200400150724
Conus venoms: A rich source of novel ion channel-targeted peptides.
AUTHOR: Terlau Heinrich; Olivera Baldomero M (Reprint)
AUTHOR ADDRESS: Dept. of Biology, Univ. of Utah, 257 South 1400 Est, Salt Lake City, UT, 84112, USA**USA
AUTHOR E-MAIL ADDRESS: olivera@biology.utah.edu
JOURNAL: Physiological Reviews 84 (1): p41-68 January 2004 2004
MEDIUM: print
ISSN: 0031-9333 _(ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

2/7/5
DIALOG(R)File 5:Biosis Previews(R)

0014703169 BIOSIS NO.: 200400069425
The binding of %%%kappa%%%-%%%Conotoxin%%% PVIIA and fast C-type inactivation of Shaker K+ channels are mutually exclusive.
AUTHOR: Koch E Dietlind; Olivera Baldomero M; Terlau Heinrich (Reprint); Conti Franco
AUTHOR ADDRESS: Molecular and Cellular Neuropharmacology Group, Max-Planck-Institute for Experimental Medicine, Hermann-Rein-Str. 3, D-37075, Goettingen, Germany**Germany
AUTHOR E-MAIL ADDRESS: hterlau@gwdg.de
JOURNAL: Biophysical Journal 86 (1 Part 1): p191-209 January 2004 2004
MEDIUM: print
ISSN: 0006-3495 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%Conotoxin%%% PVIIA (kappa-PVIIA), a 27-amino acid peptide identified from the venom of Conus purpurascens, inhibits the Shaker K+ channel by blocking its outer pore. The toxin appears as a gating modifier because its binding affinity decreases with relatively fast kinetics upon channel opening, but there is no indication that it interferes with the gating transitions of the wild-type channels (WT), including the structural changes of the outer pore that underlie its slow C-type inactivation. In this report we demonstrate that in two outer pore mutants of Shaker-IR (M448K and T449S), that have high toxin sensitivity

and fast C-type inactivation, the latter process is instead antagonized by and incompatible with kappa-PVIIA binding. Inactivation is slowed by the necessary preliminary unbinding of kappa-PVIIA, whereas toxin rebinding must await recovery from inactivation causing a double-exponential relaxation of the second response to double-pulse stimulations. Compared with the lack of similar effects in WT, these results demonstrate the ability of peptide toxins like kappa-PVIIA to reveal possibly subtle differences in structural changes of the outer pore of K+ channels; however, they also warn against a naive use of fast inactivating mutants as models for C-type inactivation. Unfolded from the antagonistic effect of inactivation, toxin binding to mutant noninactivated channels shows state- and voltage-dependencies similar to WT: slow and high affinity for closed channels; relatively fast dissociation from open channels at rate increasing with voltage. This supports the idea that these properties depend mainly on interactions with pore-permeation processes that are not affected by the mutations. In mutant channels the state-dependence also greatly enhances the protection of toxin binding against steady-state inactivation at low depolarizations while still allowing large responses to depolarizing pulses that relieve toxin block. Although not obviously applicable to any known combination of natural channel and outer-pore blocker, our biophysical characterization of such highly efficient mechanism of protection from steady-state outer-pore inactivation may be of general interest.

2/7/6
DIALOG(R)File 5:Biosis Previews(R)

0014467742 BIOSIS NO.: 200300422586
%%%kappa%%%-%%%Conotoxin%%%-PVIIA is a K-channel pore blocker toxin that does not alter slow inactivation.
AUTHOR: Naranjo David (Reprint)
AUTHOR ADDRESS: Centro de Neurociencias de Valparaiso, Universidad de Valparaiso, Gran Bretana 1111, Playa Ancha, Valparaiso, Chile**Chile
JOURNAL: Biophysical Journal 84 (2 Part 2): p77a February 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 47th Annual Meeting of the Biophysical Society San Antonio, TX, USA March 01-05, 2003; 20030301
SPONSOR: Biophysical Society
ISSN: 0006-3495 (ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/7
DIALOG(R)File 5:Biosis Previews(R)

0014295213 BIOSIS NO.: 200300253932
A novel conotoxin from Conus betulinus, kappa-BtX, unique in cysteine pattern and in function as a specific BK channel modulator.
AUTHOR: Fan Chong-xu; Chen Xiao-Ke; Zhang Chen; Wang Li-Xiu; Duan Kai-Lai; He Lin-Lin; Cao Ying; Liu Shang-Yi; Zhong Ming-nai; Ulens Chris; Tytgat Jan; Chen Ji-sheng (Reprint); Chi Cheng-Wu; Zhou Zhuan
AUTHOR ADDRESS: Research Institute of Pharmaceutical Chemistry, Beijing,

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JOURNAL: Journal of Biological Chemistry 278 (15): p12624-12633 April 11, 2003 2003
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A novel conotoxin, %%%kappa%%%-%%%conotoxin%%% (kappa-BtX), has been purified and characterized from the venom of a worm-hunting cone snail, Conus betulinus. The toxin, with four disulfide bonds, shares no sequence homology with any other conotoxins. Based on a partial amino acid sequence, its cDNA was cloned and sequenced. The deduced sequence consists of a 26-residue putative signal peptide, a 31-residue mature toxin, and a 13-residue extra peptide at the C terminus. The extra peptide is cleaved off by proteinase post-processing. All three Glu residues are gamma-carboxylated, one of the two Pro residues is hydroxylated at position 27, and its C-terminal residue is Pro-amidated. The monoisotopic mass of the toxin is 3569.0 Da. Electrophysiological experiments show that: 1) among voltage-gated channels, kappa-BtX is a specific modulator of K+ channels; 2) among the K channels, kappa-BtX specifically up-modulates the Ca2+- and voltage-sensitive BK channels (252+-47%); 3) its EC50 is 0.7 nM with a single binding site (Hill=0.88); 4) the time constant of wash-out is 8.3 s; and 5) kappa-BtX has no effect on single channel conductance, but increases the open probability of BK channels. It is concluded that kappa-BtX is a novel specific biotoxin against BK channels.

2/7/8
DIALOG(R)File 5:Biosis Previews(R)

0013771954 BIOSIS NO.: 200200365465
Modelling of the interaction of %%%kappa%%%-%%%conotoxin%%% PVIIA to the shaker potassium channel
AUTHOR: Moran Oscar (Reprint)
AUTHOR ADDRESS: Istituto di Cibernetica e Biofisica, CNR, Via De Marini, 6, Genova, I-16149, Italy**Italy
JOURNAL: Biophysical Journal 82 (1 Part 2): p628a-629a January, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 46th Annual Meeting of the Biophysical Society San Francisco, California, USA February 23-27, 2002; 20020223
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/9
DIALOG(R)File 5:Biosis Previews(R)

0013769557 BIOSIS NO.: 200200363068
Influence of potassium and rubidium on the binding of k-conotoxin PVIIA to

Shaker K+ channels
AUTHOR: Boccaccio A (Reprint); Conti F (Reprint); Olivera B M (Reprint); Terlau H (Reprint)
AUTHOR ADDRESS: Molekulare and Zellulaere Neuropharmakologie, Max-Planck-Institut fuer Experimentelle Medizin, Hermann-Rein-Str. 3, D-37075, Goettingen, Germany**Germany
JOURNAL: Pfluegers Archiv European Journal of Physiology 443 (Supplement 1): pS279 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 81st Annual Joint Meeting of the Physiological Society, the Scandinavian Physiological Society and the German Physiological Society Tuebingen, Germany March 15-19, 2002; 20020315
ISSN: 0031-6768
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/10
DIALOG(R)File 5:Biosis Previews(R)

0013769556 BIOSIS NO.: 200200363067
K+-dependence of k-conotoxin PVIIA binding to Shaker K+-channels with fast C-type inactivation
AUTHOR: Koch E D (Reprint); Conti F (Reprint); Olivera B M (Reprint); Terlau H (Reprint)
AUTHOR ADDRESS: Molekulare and Zellulaere Neuropharmakologie, Max-Planck-Institut fuer Experimentelle Medizin, 37075, Goettingen, Germany**Germany
JOURNAL: Pfluegers Archiv European Journal of Physiology 443 (Supplement 1): pS279 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 81st Annual Joint Meeting of the Physiological Society, the Scandinavian Physiological Society and the German Physiological Society Tuebingen, Germany March 15-19, 2002; 20020315
ISSN: 0031-6768
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/11
DIALOG(R)File 5:Biosis Previews(R)

0013748392 BIOSIS NO.: 200200341903
Inhibition of single Shaker K channels by %%%kappa%%%-%%%Conotoxin%%%-PVIIA
AUTHOR: Naranjo David (Reprint)
AUTHOR ADDRESS: Instituto de Fisiologia Celular, Universidad Nacional Autonoma de Mexico, Circuito Exterior, Ciudad Universitaria, 04510, Mexico, DF, Mexico**Mexico
JOURNAL: Biophysical Journal 82 (6): p3003-3011 June, 2002 2002
MEDIUM: print
ISSN: 0006-3495
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%Conotoxin%%%-PVIIA (kappa-PVIIA) is a 27-residue basic (+4) peptide from the venom of the predator snail Conus purpurascens. A single kappa-PVIIA molecule interrupts ion conduction by binding to the external mouth of Shaker K channels. The blockade of Shaker by kappa-PVIIA was studied at the single channel level in membrane patches from Xenopus oocytes. The amplitudes of blocked and closed events were undistinguishable, suggesting that the toxin interrupts ion conduction completely. Between -20 and 40 mV kappa-PVIIA increased the latency to the first opening by one order of magnitude in a concentration-independent fashion. Because kappa-PVIIA has higher affinity for the closed channels at high enough concentration to block >90% of the resting channels, the dissociation rate could be estimated from the analysis of the first latency. At 0 mV, the dissociation rate was 20 s-1 and had an effective valence of 0.64. The apparent closing rate increased linearly with (kappa-PVIIA) indicating an association rate of 56 muM-1 s-1. The toxin did not modify the fraction of null traces. This result suggests that the structural rearrangements in the external mouth contributing to the slow inactivation preserve the main geometrical features of the toxin-receptor interaction.

2/7/12
DIALOG(R)File 5:Biosis Previews(R)

0013719120 BIOSIS NO.: 200200312631
The interaction of %%%kappa%%%-%%%conotoxin%%% PVIIA with Shaker K+-channels is mediated differently by K+ and RB+
AUTHOR: Boccaccio Anna (Reprint); Conti Franco; Olivera Baldomero M; Terlau Heinrich (Reprint)
AUTHOR ADDRESS: Max Planck Inst. fuer Exp. Med., Hermann-Rein Str.3, Goettingen, 37075, Germany**Germany
JOURNAL: Biophysical Journal 82 (1 Part 2): p235a January, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 46th Annual Meeting of the Biophysical Society San Francisco, California, USA February 23-27, 2002; 20020223
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/13
DIALOG(R)File 5:Biosis Previews(R)

0013545620 BIOSIS NO.: 200200139131
Molecular simulation of the interaction of %%%kappa%%%-%%%conotoxin%%% -PVIIA with the Shaker potassium channel pore
AUTHOR: Moran Oscar (Reprint)
AUTHOR ADDRESS: Istituto di Cibernetica e Biofisica, CNR, Via De Marini 6, 16149, Genoa, Italy**Italy
JOURNAL: European Biophysics Journal 30 (7): p528-536 December, 2001 2001
MEDIUM: print
ISSN: 0175-7571

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Molecular simulation techniques were applied to predict the interaction of the voltage-dependent Shaker potassium channel with the channel-blocking toxin %%%kappa%%%-%%%conotoxin%%%-PVIIA (PVIIA). A structural three-dimensional model of the extracellular vestibule of the potassium channel was constructed based on structural homologies with the bacterial potassium channel Kcsa, whose structure has been solved by X-ray crystallography. The docking of the PVIIA molecule was obtained by a geometric recognition algorithm, yielding 100 possible conformations. A series of residue-residue distance restraints, predicted from mutation-cycle experiments, were used to select a small set of a plausible channel-toxin complex models among the resulting possible conformations. The four final conformations, with similar characteristics, can explain most of the single-point mutation experiments done with this system. The models of the Shaker-PVIIA interaction predict two clusters of amino acids, critical for the binding of the toxin to the channel. The first cluster is the amino acids R2, I3, Q6 and K7 that form the plug of the toxin that interacts with the entrance to the selectivity filter of the channel. The second cluster of residues, R22, F23, N24 and K25, interacts with a channel region near to the external entrance of the pore vestibule. The consistency of the obtained models and the experimental data indicate that the Shaker-PVIIA complex model is reasonable and can be used in further biological studies such as the rational design of blocking agents of potassium channels and the mutagenesis of both toxins and potassium channels.

2/7/14
DIALOG(R)File 5:Biosis Previews(R)

0013490751 BIOSIS NO.: 200200084262
Conotoxin peptide PVIIA
AUTHOR: Terlau H; Shon K-J; Grilley M; Olivera B M
AUTHOR ADDRESS: Goettingen, Germany**Germany
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1202 (5): p3900 Sept. 30, 1997 1997
MEDIUM: print
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Citation
LANGUAGE: English

2/7/15
DIALOG(R)File 5:Biosis Previews(R)

0013409305 BIOSIS NO.: 200200002816
%%%kappa%%%-%%%Conotoxin%%% PVIIA binding to Shaker K-channels and fast C-type inactivation are mutually exclusive
AUTHOR: Koch E D (Reprint); Conti F; Olivera B M; Terlau H (Reprint)
AUTHOR ADDRESS: Max-Planck-Institute for Experimental Medicine, Goettingen, Germany**Germany

JOURNAL: Society for Neuroscience Abstracts 27 (2): p2147 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
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DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%conotoxin%%% PVIIA (kappa-PVIIA), a 27 amino acid peptide from the venom of the predatory marine cone snail Conus purpurascens, is the first member of a family of conotoxins blocking voltage-gated K-channels. Physiologically it seems to play a key role in the extremely rapid immobilization of the fish prey. kappa-PVIIA binds to the outer vestibule of the ion channel pore of Shaker K-channels and interacting amino acids have been identified. The binding reaction is state dependent: the affinities differ for the open (conducting) and closed or N-type inactivated (non-conducting) states. By using the Xenopus oocyte expression system we here studied the interaction of kappa-PVIIA to a pore mutant (M448K) of the Shaker K-channel. In the absence of N-type inactivation (DELTA 6-46), this channel displays rapid C-type inactivation with a time constant of apprx17 ms at 0 mV. The state-dependence of kappa-PVIIA binding to M448K is conserved. The affinity to the closed state is similar to that of wild-type channels (IC50 apprx80 nM vs. apprx50 nM, respectively) whereas the IC50 for the open state at 0 mV (apprx1 muM) is 5 times higher than for wild-type channels. However, the presence of kappa-PVIIA apparently slows the inactivation and the total current flowing during a depolarizing pulse is not reduced by the toxin. Interestingly, under certain conditions kappa-PVIIA can even lead to a dramatic increase in the amount of current. We conclude that binding of kappa-PVIIA and fast C-type inactivation in mutant Shaker K-channels are mutually exclusive.

2/7/16
DIALOG(R)File 5:Biosis Previews(R)

0013083122 BIOSIS NO.: 200100254961
Fast C-type inactivation abolishes the affinity of %%%kappa%%%-%%%conotoxin%%% PVIIA to Shaker K+-channels
AUTHOR: Koch E D (Reprint); Conti F; Olivera B M; Terlau H (Reprint)
AUTHOR ADDRESS: Max-Planck-Institut fuer Experimentelle Medizin, Molekulare and Zellulaere Neuropharmakologie, 37075, Goettingen, Germany**Germany
JOURNAL: Pfluegers Archiv European Journal of Physiology 441 (6 Supplement): pR142 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Joint Congress of the Scandinavian and the German Physiological Societies Berlin, Germany March 10-13, 2001; 20010310
ISSN: 0031-6768
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/17
DIALOG(R)File 5:Biosis Previews(R)

0013003226 BIOSIS NO.: 200100175065
Inhibition of K-channels by %%%kappa%%%-%%%conotoxin%%%-PVIIA at microscopic level
AUTHOR: Naranjo David (Reprint); Garcia Esperanza
AUTHOR ADDRESS: UNAM, Circuito Exterior, CU, Mexico City, DF, 04510, Mexico **Mexico
JOURNAL: Biophysical Journal 80 (1 Part 2): p446a January, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the Biophysical Society Boston, Massachusetts, USA February 17-21, 2001; 20010217
SPONSOR: Biophysical Society
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/18
DIALOG(R)File 5:Biosis Previews(R)

0012979020 BIOSIS NO.: 200100150859
Variability in automated assignment of NOESY spectra and three-dimensional structure determination: A test case on three small disulfide-bonded proteins
AUTHOR: Savarin Philippe; Zinn-Justin Sophie; Gilquin Bernard (Reprint)
AUTHOR ADDRESS: Departement d'Ingenierie et d'Etudes des Proteines, CEA-Saclay, Bat. 152, F-91191, Gif-sur-Yvette Cedex, France**France
JOURNAL: Journal of Biomolecular NMR 19 (1): p49-62 January, 2001 2001
MEDIUM: print
ISSN: 0925-2738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Three independent runs of automatic assignment and structure calculations were performed on three small proteins, calcicludine from the venom of the green mamba Dendroaspis angusticeps, %%%kappa%%%-%%%conotoxin%%% PVIIA from the purple cone Conus purpurascens and HsTX1, a short scorpion toxin from the venom of Heterometrus spinnifer. At the end of all the runs, the number of cross peaks which remained unassigned (0.6%, 1.4% and 2% for calcicludine, %%%kappa%%%-%%%conotoxin%%% and HsTX1, respectively), as well as the number of constraints which were rejected as producing systematic violations (2.7%, 1.0%, and 1.4% for calcicludine, %%%kappa%%%-%%%conotoxin%%% and HsTX1, respectively) were low. The conformation of the initial model used in the procedure (linear model or constructed by homology) has no influence on the final structures. Mainly two parameters control the procedure: the chemical shift tolerance and the cut-off distance. Independent runs of structure calculations, using the same parameters, yield structures for which the rmsd between averaged structures and the rmsd around each averaged structure were of the same order of magnitude. A different cut-off distance and a different chemical shift tolerance yield rmsd values on final average structures which did not differ more than 0.5 ANG compared to the rmsd obtained around the averaged structure for each calculation.

These results show that the procedure is robust when applied to such a small disulfide-bonded protein.

2/7/19
DIALOG(R)File 5:Biosis Previews(R)

0012951115 BIOSIS NO.: 200100122954
A novel family of lambda-conotoxin characterized from venom of marine snail Conus marmoreus
AUTHOR: Balaji R Ashok (Reprint); Ohtake Atsuko; Gopalakr-Ishnakone P (Reprint); Sato Kazuki; Kini R Manjunatha; Bay Boon-Huat (Reprint)
AUTHOR ADDRESS: Venom and Toxin Research Programme, Faculty of Medicine, National University of Singapore, Singapore, 117597, Republic of Singapore**Republic of Singapore
JOURNAL: Biochemical Society Transactions 28 (5): pA409 October, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 18th International Congress of Biochemistry and Molecular Biology Birmingham, UK July 16-20, 2000; 20000716
SPONSOR: International Union of Biochemistry and Molecular Biology
Federation of European Biochemical Societies
Biochemical Society
ISSN: 0300-5127
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/20
DIALOG(R)File 5:Biosis Previews(R)

0012920429 BIOSIS NO.: 200100092268
Solution structure of HpTX2, a toxin from Heteropoda venatoria spider that blocks Kv4.2 potassium channel
AUTHOR: Bernard Cedric; Legros Christian; Ferrat Gilles; Bischoff Ulrike; Marquardt Annette; Pongs Olaf; Darbon Herve (Reprint)
AUTHOR ADDRESS: AFMB-UPR 9030, CNRS IFR1, 31 Chemin Joseph-Aiguier, Marseille Cedex, 13402, France**France
JOURNAL: Protein Science 9 (11): p2059-2067 November, 2000 2000
MEDIUM: print
ISSN: 0961-8368
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: HpTX2 is a toxin from the venom of Heteropoda venatoria spider that has been demonstrated to bind on Kv4.2 potassium channel. We have determined the solution structure of recombinant HpTX2 by use of conventional two-dimensional NMR techniques followed by distance-geometry and molecular dynamics. The calculated structure belongs to the Inhibitory Cystin Knot structural family that consists in a compact disulfide-bonded core, from which four loops emerge. A poorly defined two-stranded antiparallel beta-sheet (residues 20-23 and 25-28) is detected. Analysis of the electrostatic charge anisotropy allows us to propose a functional map of HpTX2 different from the one described for

%%%kappa%%%-%%%conotoxin%%% PVIIA, but strongly related to the one of charybdotoxin. The orientation of the dipole moment of HpTX2 emerges through K27 which could therefore be the critical lysine residue. Close to this lysine are a second basic residue, R23, an aromatic cluster (F7, W25, W30) and an hydrophobic side chain (L24). The high density in aromatic side chains of the putative functional surface as well as the lack of an asparagine is proposed to be the structural basis of the specificity of HpTX2 toward Kv4.2 channel.

2/7/21
DIALOG(R)File 5:Biosis Previews(R)

0012733444 BIOSIS NO.: 200000451757
The interaction of %%%kappa%%%-%%%conotoxin%%% PVIIA with Shaker K+-channels: Dependence on monovalent cations
AUTHOR: Boccaccio A (Reprint); Terlau H (Reprint); Olivera B M; Conti F
AUTHOR ADDRESS: MPI fuer Exp Med, Hermann-Rein-Strasse 3, 37075, Goettingen, Germany**Germany
JOURNAL: European Biophysics Journal 29 (4-5): p344 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 3rd European Biophysics Congress Munchen, Germany September 09-13, 2000; 20000909
ISSN: 0175-7571
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/22
DIALOG(R)File 5:Biosis Previews(R)

0012698972 BIOSIS NO.: 200000417285
Single amino acid substitutions in %%%kappa%%%-%%%conotoxin%%% PVIIA disrupt interaction with the Shaker K+ channel
AUTHOR: Jacobsen Richard B; Koch E Dietlind; Lange-Malecki Bettina; Stocker Martin; Verhey Janko; Van Wagoner Ryan M; Vyazovkina Alexandra; Olivera Baldomero M (Reprint); Terlau Heinrich
AUTHOR ADDRESS: Dept. of Biology, University of Utah, 257 S. 1400 E. 201, Salt Lake City, UT, 84112-0840, USA**USA
JOURNAL: Journal of Biological Chemistry 275 (32): p24639-24644 August 11, 2000 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%Conotoxin%%% PVIIA (kappa-PVIIA), a 27-amino acid peptide with three disulfide cross-links, isolated from the venom of Conus purpurascens, is the first conopeptide shown to inhibit the Shaker K+ channel (Terlau, H., Shon, K., Grilley, M., Stocker, M., Stuhmer, W., and Olivera, B. M. (1996) Nature 381, 148-151). Recently, two groups independently determined the solution structure for kappa-PVIIA using NMR; although the structures reported were similar, two mutually

exclusive models for the interaction of the peptide with the Shaker channel were proposed. We carried out a structure/function analysis of kappa-PVIIA, with alanine substitutions for all amino acids postulated to be key residues by both groups. Our data are consistent with the critical dyad model developed by Menez and co-workers (Dauplais, M., Lecoq, A., Song, J., Cotton, J., Jamin, N., Gilquin, B., Roumestand, C., Vita, C., de Medeiros, C., Rowan, E. G., Harvey, A. L., and Menez, A. (1997) J. Biol. Chem. 272, 4802-4809) for polypeptide antagonists of K+ channels. In the case of kappa-PVIIA, Lys7 and Phe9 are essential for activity as predicted by Savarin et al. (Savarin, P., Guenneugues, M., Gilquin, B., Lamthanh, H., Gasparini, S., Zinn-Justin, S., and Menez, A. (1998) Biochemistry 37, 5407-5416); these workers also correctly predicted an important role for Lys25. Thus, although %%%kappa%%%-%%%conotoxin%%% PVIIA has no obvious sequence homology to polypeptide toxins from other venomous animals that interact with voltage-gated K+ channels, there may be convergent functional features in diverse K+ channel polypeptide antagonists.

2/7/23
DIALOG(R)File 5:Biosis Previews(R)

0012688547 BIOSIS NO.: 200000406860
Conotoxin TVIIA, a novel peptide from the venom of Conus tulipa. 2. Three-dimensional solution structure
AUTHOR: Hill Justine M; Alewood Paul F; Craik David J (Reprint)
AUTHOR ADDRESS: Centre for Drug Design and Development, Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, 4072, Australia**Australia
JOURNAL: European Journal of Biochemistry 267 (15): p4649-4657 August, 2000 2000
MEDIUM: print
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The three-dimensional solution structure of conotoxin TVIIA, a 30-residue polypeptide from the venom of the piscivorous cone snail Conus tulipa, has been determined using 2D 1H NMR spectroscopy. TVIIA contains six cysteine residues which form a 'four-loop' structural framework common to many peptides from Conus venoms including the omega-, delta-, kappa-, and muO-conotoxins. However, TVIIA does not belong to these well-characterized pharmacological classes of conotoxins, but displays high sequence identity with conotoxin GS, a muscle sodium channel blocker from Conus geographus. Structure calculations were based on 562 interproton distance restraints inferred from NOE data, together with 18 backbone and nine side-chain torsion angle restraints derived from spin-spin coupling constants. The final family of 20 structures had mean pairwise rms differences over residues 2-27 of 0.18 +- 0.05 ANG for the backbone atoms and 1.39 +- 0.33 ANG for all heavy atoms. The structure consists of a triple-stranded, antiparallel beta sheet with +2x, -1 topology (residues 7-9, 16-20 and 23-27) and several beta turns. The core of the molecule is formed by three disulfide bonds which form a cystine knot motif common to many toxic and inhibitory polypeptides. The global fold, molecular shape and distribution of amino-acid sidechains in TVIIA

is similar to that previously reported for conotoxin GS, and comparison with other four-loop conotoxin structures provides further indication that TVIIA and GS represent a new and distinct subgroup of this structural family. The structure of TVIIA determined in this study provides the basis for determining a structure-activity relationship for these molecules and their interaction with target receptors.

2/7/24
DIALOG(R)File 5:Biosis Previews(R)

0012688546 BIOSIS NO.: 200000406859
Conotoxin TVIIA, a novel peptide from the venom of Conus tulipa. 1. Isolation, characterization and chemical synthesis
AUTHOR: Hill Justine M; Atkins Annette R; Loughnan Marion L; Jones Alun; Adams Denise A; Martin Rod C; Lewis Richard J; Craik David J; Alewood Paul F (Reprint)
AUTHOR ADDRESS: Centre for Drug Design and Development, Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, 4072, Australia**Australia
JOURNAL: European Journal of Biochemistry 267 (15): p4642-4648 August, 2000 2000
MEDIUM: print
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A novel conotoxin belonging to the 'four-loop' structural class has been isolated from the venom of the piscivorous cone snail Conus tulipa. It was identified using a chemical-directed strategy based largely on mass spectrometric techniques. The new toxin, conotoxin TVIIA, consists of 30 amino-acid residues and contains three disulfide bonds. The amino-acid sequence was determined by Edman analysis as SCSGRDSRCOOVCCMGLMCSRGKCVSIYGE where O = 4-trans-L-hydroxyproline. Two under-hydroxylated analogues, (Pro10)TVIIA and (Pro10,11)TVIIA, were also identified in the venom of C. tulipa. The sequences of TVIIA and (Pro10)TVIIA were further verified by chemical synthesis and coelution studies with native material. Conotoxin TVIIA has a six cysteine/four-loop structural framework common to many peptides from Conus venoms including the omega-, delta- and %%%kappa%%%-%%%conotoxins%%%. However, TVIIA displays little sequence homology with these well-characterized pharmacological classes of peptides, but displays striking sequence homology with conotoxin GS, a peptide from Conus geographus that blocks skeletal muscle sodium channels. These new toxins and GS share several biochemical features and represent a distinct subgroup of the four-loop conotoxins.

2/7/25
DIALOG(R)File 5:Biosis Previews(R)

0012509773 BIOSIS NO.: 200000228086
A marine snail %%%kappa%%%-%%%conotoxin%%% blocks the pore of K+ channels as alpha-KTX scorpion toxins do

AUTHOR: Naranjo David (Reprint); Garcia Esperanza (Reprint)
AUTHOR ADDRESS: Instituto de Fisiologia Celular, Circuito Exterior, UNAM, Ciudad Universitaria, 04510, Mexico, DF, Mexico**Mexico
JOURNAL: Journal of Physiology (Cambridge) (523P): p2S-3S Feb., 2000 2000
MEDIUM: print
CONFERENCE/MEETING: Joint Meetings of the Physiological Society. Birmingham, England, UK December 20-22, 1999; 19991220
SPONSOR: The Physiological Society
ISSN: 0022-3751
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/26
DIALOG(R)File 5:Biosis Previews(R)

0012435237 BIOSIS NO.: 200000153550
Ionic strength affects differentially the binding of %%%kappa%%%-%%%conotoxin%%%-pviia to open and closed Shaker K-channels
AUTHOR: Naranjo David (Reprint); Hernandez Consuelo; Garcia Esperanza
AUTHOR ADDRESS: Universidad Nacional Autonoma de Mexico, Circuito Exterior s/n, Ciudad Universitaria, Mexico, DF, 04510, Mexico**Mexico
JOURNAL: Biophysical Journal 78 (1 Part 2): p97A Jan., 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the Biophysical Society. New Orleans, Louisiana, USA February 12-16, 2000; 20000212
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/27
DIALOG(R)File 5:Biosis Previews(R)

0012418895 BIOSIS NO.: 200000137208
Interaction of %%%kappa%%%-%%%conotoxin%%% PVIIA with the Shaker potassium channel
AUTHOR: Koch E D (Reprint); Terlau H (Reprint); Olivera B M
AUTHOR ADDRESS: Max-Planck-Institut fuer Experimentelle Medizin, D-37075, Goettingen, Germany**Germany
JOURNAL: Society for Neuroscience Abstracts 25 (1-2): p1986 1999 1999
MEDIUM: print
CONFERENCE/MEETING: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999; 19991023
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
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LANGUAGE: English

2/7/28
DIALOG(R)File 5:Biosis Previews(R)

0012127174 BIOSIS NO.: 199900386834
A marine snail neurotoxin shares with scorpion toxins a convergent mechanism of blockade on the pore of voltage-gated K channels
AUTHOR: Garcia Esperanza; Scanlon Martin; Naranjo David (Reprint)
AUTHOR ADDRESS: Instituto de Fisiologia Celular, UNAM, Circuito Exterior, Ciudad Universitaria, 04510, Mexico, DF, Mexico**Mexico
JOURNAL: Journal of General Physiology 114 (1): p141-157 July, 1999 1999
MEDIUM: print
ISSN: 0022-1295
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%Conotoxin%%%-PVIIA (kappa-PVIIA) belongs to a family of peptides derived from a hunting marine snail that targets to a wide variety of ion channels and receptors. kappa-PVIIA is a small, structurally constrained, 27-residue peptide that inhibits voltage-gated K channels. Three disulfide bonds shape a characteristic four-loop folding. The spatial localization of positively charged residues in kappa-PVIIA exhibits strong structural mimicry to that of charybdotoxin, a scorpion toxin that occludes the pore of K channels. We studied the mechanism by which this peptide inhibits Shaker K channels expressed in Xenopus oocytes with the N-type inactivation removed. Chronically applied to whole oocytes or outside-out patches, kappa-PVIIA inhibition appears as a voltage-dependent relaxation in response to the depolarizing pulse used to activate the channels. At any applied voltage, the relaxation rate depended linearly on the toxin concentration, indicating a bimolecular stoichiometry. Time constants and voltage dependence of the current relaxation produced by chronic applications agreed with that of rapid applications to open channels. Effective valence of the voltage dependence, zdelta, is apprx0.55 and resides primarily in the rate of dissociation from the channel, while the association rate is voltage independent with a magnitude of 107-108 M-1 s-1, consistent with diffusion-limited binding. Compatible with a purely competitive interaction for a site in the external vestibule, tetraethylammonium, a well-known K-pore blocker, reduced kappa-PVIIA's association rate only. Removal of internal K+ reduced, but did not eliminate, the effective valence of the toxin dissociation rate to a value <0.3. This trans-pore effect suggests that: (a) as in the alpha-KTx, a positively charged side chain, possibly a Lys, interacts electrostatically with ions residing inside the Shaker pore, and (b) a part of the toxin occupies an externally accessible K+ binding site, decreasing the degree of pore occupancyby permeant ions. We conclude that, although evolutionarily distant to scorpion toxins, kappa-PVIIA shares with them a remarkably similar mechanism of inhibition of K channels.

2/7/29
DIALOG(R)File 5:Biosis Previews(R)

0012127173 BIOSIS NO.: 199900386833
The block of Shaker K+ channels by %%%kappa%%%-%%%conotoxin%%% PVIIA is state dependent
AUTHOR: Terlau Heinrich; Boccaccio Anna; Olivera Baldomero M; Conti Franco

(Reprint)
AUTHOR ADDRESS: Istituto di Cibernetica e Biofisica, CNR, 16149, Genova, Italy**Italy
JOURNAL: Journal of General Physiology 114 (1): p125-140 July, 1999 1999
MEDIUM: print
ISSN: 0022-1295
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%conotoxin%%% PVIIA is the first conotoxin known to interact with voltage-gated potassium channels by inhibiting Shaker-mediated currents. We studied the mechanism of inhibition and concluded that PVIIA blocks the ion pore with a 1:1 stoichiometry and that binding to open or closed channels is very different. Open-channel properties are revealed by relaxations of partial block during step depolarizations, whereas double-pulse protocols characterize the slower reequilibration of closed-channel binding. In 2.5 mM-(K+)o, the IC50 rises from a tonic value of apprx50 to apprx200 nM during openings at 0 mV, and it increases e-fold for about every 40-mV increase in voltage. The change involves mainly the voltage dependence and a 20-fold increase at 0 mV of the rate of PVIIA dissociation, but also a fivefold increase of the association rate. PVIIA binding to Shaker DELTA6-46 channels lacking N-type inactivation or to wild phenotypes appears similar, but inactivation partially protects the latter from open-channel unblock. Raising (K+)o to 115 mM has little effect on open-channel binding, but increases almost 10-fold the tonic IC50 of PVIIA due to a decrease by the same factor of the toxin rate of association to closed channels. In analogy with charybdotoxin block, we attribute the acceleration of PVIIA dissociation from open channels to the voltage-dependent occupancy by K+ ions of a site at the outer end of the conducting pore. We also argue that the occupancy of this site by external cations antagonizes on binding to closed channels, whereas the apparent competition disappears in open channels if the competing cation can move along the pore. It is concluded that PVIIA can also be a valuable tool for probing the state of ion permeation inside the pore.

2/7/30
DIALOG(R)File 5:Biosis Previews(R)

0011926419 BIOSIS NO.: 199900186079
The interaction of %%%kappa%%%-%%%conotoxin%%% PVIIA with Shaker K+-channels is state dependent
AUTHOR: Terlau H (Reprint); Boccaccio A (Reprint); Olivera B M; Conti F
AUTHOR ADDRESS: Max Planck Institut fuer Experimentelle Medizin, Goettingen, Germany**Germany
JOURNAL: Biophysical Journal 76 (1 PART 2): pA150 Jan., 1999 1999
MEDIUM: print
CONFERENCE/MEETING: Forty-third Annual Meeting of the Biophysical Society Baltimore, Maryland, USA February 13-17, 1999; 19990213
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/31
DIALOG(R)File 5:Biosis Previews(R)

0011824566 BIOSIS NO.: 199900084226
Purification and partial characterization of a 'short' insectotoxin-like peptide from the venom of the scorpion Parabuthus schlechteri
AUTHOR: Tytgat Jan (Reprint); Debont Tom; Rostoll Karin; Mueller Gert J; Verdonck Fons; Daenens Paul; Van Der Walt Jurg J; Possani Lourival D
AUTHOR ADDRESS: Lab. Toxicol., Univ. Levuen, E. Van Evenstr. 4, B-3000 Leuven, Belgium**Belgium
JOURNAL: FEBS Letters 441 (3): p387-391 Dec. 28, 1998 1998
MEDIUM: print
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A disulfide-rich, low-molecular-mass toxin-like peptide has been isolated from Parabuthus schlechteri venom using gel filtration, ion exchange, and reversed phase chromatography. Partial characterization of this peptide reveals a relationship with four-disulfide bridge proteins belonging to the family of 'short' insectotoxins (44% residue identity). In recognition hereof, the peptide was named PBITx1 (sITx10). Our work also reports on the deduced sequences of two other 'short' insectotoxins from Buthus eupeus, I3 and I4, and it provides a consensus sequence and nomenclature for all known 'short' insectotoxins. Finally, sequence similarities with K+ channel blockers (charybdotoxin, %%%kappa%%%-%%%conotoxin%%%), and a Cl- channel blocker (chlorotoxin) are highlighted.

2/7/32
DIALOG(R)File 5:Biosis Previews(R)

0011724358 BIOSIS NO.: 199800518605
The cystine knot structure of ion channel toxins and related polypeptides
AUTHOR: Norton Raymond S (Reprint); Pallaghy Paul K
AUTHOR ADDRESS: Biomol. Res. Inst., 343 Royal Parade, Parkville, 3052, Australia**Australia
JOURNAL: Toxicon 36 (11): p1573-1583 Nov., 1998 1998
MEDIUM: print
ISSN: 0041-0101
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: An increasing number of ion channel toxins and related polypeptides have been found to adopt a common structural motif designated the inhibitor cystine knot motif (Pallaghy P. K., Nielsen, K. J., Craik, D. J, Norton, R. S. (1994) A common structural motif incorporating a cystine knot and triple-stranded beta-sheet in toxic and inhibitory polypeptides. Protein Science 3, 1833-1839). These globular, disulfide-stabilized molecules come from phylogenetically diverse sources, including spiders, cone shells, plants and fungi, and have

various functions, although many target voltage-gated ion-channels. The common motif consists of a cystine knot and a triple-stranded, anti-parallel beta-sheet. Examples of ion-channel toxins known to adopt this structure are the omega-conotoxins and omega-agatoxins, and, more recently, robustoxin, versutoxin and protein 5 from spiders, as well as %%%kappa%%%-%%%conotoxin%%% PVIIA and conotoxin GS from cone shells. The variations on the motif structure exemplified by these structures are described here. We also consider the sequences of several polypeptides that might adopt this fold, including SNX-325 from a spider, delta-conotoxin PVIA and the muO-conotoxins from cone shells, and various plant and fungal polypeptides. The interesting case of the two- and three-disulfide bridged binding domains of the cellobiohydrolases from the fungus Trichoderma reesei is also discussed. The compact and robust nature of this motif makes it an excellent scaffold for the design and engineering of novel polypeptides with enhanced activity against existing targets, or with activity against novel targets.

2/7/33
DIALOG(R)File 5:Biosis Previews(R)

0011470805 BIOSIS NO.: 199800265052
Three-dimensional structure of %%%kappa%%%-%%%conotoxin%%% PVIIA, a novel potassium channel-blocking toxin from cone snails
AUTHOR: Savarin Philippe; Guenneugues Marc; Gilquin Bernard; Lamthanh Hung; Gasparini Sylvaine; Zinn-Justin Sophie (Reprint); Menez Andre
AUTHOR ADDRESS: CEA, Dep. Ingenierie Etudes Proteines, CE Saclay, 91191 Gif-sur-Yvette Cedex, France**France
JOURNAL: Biochemistry 37 (16): p5407-5416 April 21, 1998 1998
MEDIUM: print
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%%-%%%Conotoxin%%% PVIIA from the venom of Conus purpurascens is the first cone snail toxin that was described to block potassium channels. We synthesized chemically this toxin and showed that its disulfide bridge pattern is similar to those of omega- and delta-conotoxins. %%%kappa%%%-%%%conotoxin%%% competes with radioactive alpha-dendrotoxin for binding to rat brain synaptosomes, confirming its capacity to bind to potassium channels; however, it behaves as a weak competitor. The three-dimensional structure of %%%kappa%%%-%%%conotoxin%%% PVIIA, as elucidated by NMR spectroscopy and molecular modeling, comprises two large parallel loops stabilized by a triple-stranded antiparallel beta-sheet and three disulfide bridges. The overall fold of %%%kappa%%%-%%%conotoxin%%% is similar to that of calcium channel-blocking omega-conotoxins but differs from those of potassium channel-blocking toxins from sea anemones, scorpions, and snakes. Local topographies of %%%kappa%%%-%%%conotoxin%%% PVIIA that might account for its capacity to recognize Kv1-type potassium channels are discussed.

2/7/34
DIALOG(R)File 5:Biosis Previews(R)

0011293829 BIOSIS NO.: 199800088076
Solution structure and proposed binding mechanism of a novel potassium channel toxin %%%kappa%%%-%%%conotoxin%%% PVIIA
AUTHOR: Scanlon Martin J (Reprint); Naranjo David; Thomas Linda; Alewood Paul F; Lewis Richard J; Craik David J
AUTHOR ADDRESS: Cent. Drug Design and Dev., Univ. Queensland, St. Lucia, 4072 QLD, Australia**Australia
JOURNAL: Structure (London) 5 (12): p1585-1597 Dec. 15, 1997 1997
MEDIUM: print
ISSN: 0969-2126
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: kappa-PVIIA is a 27-residue polypeptide isolated from the venom of Conus purpurascens and is the first member of a new class of conotoxins that block potassium channels. By comparison to other ion channels of eukaryotic cell membranes, voltage-sensitive potassium channels are relatively simple and methodology has been developed for mapping their interactions with small-peptide toxins. PVIIA, therefore, is a valuable new probe of potassium channel structure. This study of the solution structure and mode of channel binding of PVIIA forms the basis for mapping the interacting residues at the conotoxin-ion channel interface. Results: The three-dimensional structure of PVIIA resembles the triple-stranded beta sheet/cystine-knot motif formed by a number of toxic and inhibitory peptides. Subtle structural differences, predominantly in loops 2 and 4, are observed between PVIIA and other conotoxins with similar structural frameworks, however. Electrophysiological binding data suggest that PVIIA blocks channel currents by binding in a voltage-sensitive manner to the external vestibule and occluding the pore. Comparison of the electrostatic surface of PVIIA with that of the well-characterised potassium channel blocker charybdotoxin suggests a likely binding orientation for PVIIA. Conclusions: Although the structure of PVIIA is considerably different to that of the alphaK scorpion toxins, it has a similar mechanism of channel blockade. On the basis of a comparison of the structures of PVIIA and charybdotoxin, we suggest that Lys19 of PVIIA is the residue which is responsible for physically occluding the pore of the potassium channel.

2/7/35.
DIALOG(R)File 5:Biosis Previews(R)

0011292389 BIOSIS NO.: 199800086636
%%%kappa%%%-%%%Conotoxin%%% PVIIA is a peptide inhibiting the Shaker K+ channel
AUTHOR: Shon Ki-Joon; Stocker Martin; Terlau Heinrich; Stuehmer Walter; Jacobsen Richard; Walker Craig; Grilley Michelle; Watkins Maren; Hillyard David R; Gray William R; Olivera Baldomero M (Reprint)
AUTHOR ADDRESS: Univ. Utah, 201 S. Biology, Salt Lake City, UT 84112, USA** USA
JOURNAL: Journal of Biological Chemistry 273 (1): p33-38 Jan. 2, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%kappa%%% %%%Conotoxin%%% PVIIA (kappa-PVIIA), a 27-amino acid toxin from Conus purpurascens venom that inhibits the Shaker potassium channel, was chemically synthesized in a biologically active form. The disulfide connectivity of the peptide was determined. A structure was give for %%%kappa%%%-%%%Conotoxin%%% PVIIA. This is the first Conus peptide known to target K+ channels. Although the Shaker K+ channel is sensitive to kappa-PVIIA, the rat brain Kv1.1 subtype is resistant. Chimeras between Shaker and the Kv1.1 K+ channels were constructed and expressed in Xenopus oocytes. Only channels containing the putative pore-forming region between the fifth and sixth transmembrane domains of Shaker retained toxin sensitivity, indicating that the toxin target site is in this region of the channel. Evidence is presented that kappa-PVIIA interacts with the external tetraethyl-ammonium binding site on the Shaker channel. Although both kappa-PVIIA and charybdotoxin inhibit the Shaker channel, they must interact differently. The F425G Shaker mutation increases charybdotoxin affinity by 3 orders of magnitude but abolishes kappa-PVIIA sensitivity. The precursor sequence of kappa-PVIIA was deduced from a cDNA clone, revealing a prepropeptide comprising 72 amino acids. The N-terminal region of the K-PVIIA prepropeptide exhibits striking homology to the omega, muO-, and delta-conotoxins. Thus, at least four pharmacologically distinct superfamilies of Conus peptides belong to the same "O" superfamily, with the omega and %%%KAPPA%%%-%%%conotoxins%%% forming one branch, and the delta and muO-conotoxins forming a second major branch.

2/7/36

0011183122 BIOSIS NO.: 199799817182
Alternative splicing in the pore-forming region of shaker potassium channels
AUTHOR: Kim Marshall; Baro Deborah J; Lanning Cathy C; Doshi Mehul; Farnham Jeremy; Moskowitz Howard S; Peck Jack H; Olivera Baldomero M; Harris-Warrick Ronadl M (Reprint)
AUTHOR ADDRESS: Section Neurobiol. Behavior, Cornell Univ., Seeley G. Mudd Hall, Ithaca, NY 14853, USA**USA
JOURNAL: Journal of Neuroscience 17 (21): p8213-8224 1997 1997
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have cloned cDNAs for the shaker potassium channel gene from the spiny lobster Panulirus interruptus. As previously found in Drosophila, there is alternative splicing at the 5' and 3' ends of the coding region. However, in Panulirus shaker, alternative splicing also occurs within the pore-forming region of the protein. Three different splice variants were found within the P region, two of which bestow unique electrophysiological characteristics to channel function. Pore I and pore II variants differ in voltage dependence for activation, kinetics of inactivation, current rectification, and drug resistance. The pore 0 variant lacks a P region exon and does not produce a functional

channel. This is the first example of alternative splicing within the pore-forming region of a voltage-dependent ion channel. We used a recently identified potassium channel blocker, %%%kappa%%%-%%%conotoxin%%% PVIIA, to study the physiological role of the two pore forms. The toxin selectively blocked one pore form, whereas the other form, heteromers between the two pore forms, and Panulirus shal were not blocked. When it was tested in the Panulirus stomatogastric ganglion, the toxin produced no effects on transient K+ currents or synaptic transmission between neurons.

2/7/37
DIALOG(R)File 5:Biosis Previews(R)

0010583189 BIOSIS NO.: 199699217249
%%%Kappa%%%-%%%conotoxin%%% PVIIA, a Conus peptide targeted to potassium channels
AUTHOR: Jacobsen R (Reprint); Stocker M; Terlau H; Shon K; Grilley M (Reprint); Gray W R (Reprint); Stuhmer W; Olivera B M (Reprint)
AUTHOR ADDRESS: Dep. Biol., Univ. Utah, Salt Lake City, UT 84112, USA**USA
JOURNAL: Society for Neuroscience Abstracts 22 (1-3): p351 1996 1996
CONFERENCE/MEETING: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996; 19961116
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/38
DIALOG(R)File 5:Biosis Previews(R)

0010372885 BIOSIS NO.: 199699006945
Strategy for rapid immobilization of prey by a fish-hunting marine snail
AUTHOR: Terlau Heinrich; Shon Ki-Joon; Grilley Michelle; Stocker Martin; Stuehmer Walter; Olivera Baldomero M (Reprint)
AUTHOR ADDRESS: Dep. Biol., Univ. Utah, Salt Lake City, UT 84112, USA**USA
JOURNAL: Nature (London) 381 (6578): p148-151 1996 1996
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Some venomous animals capture prey with remarkable efficiency and speed. The purple cone, Conus purpurascens, uses two parallel physiological mechanisms requiring multiple neurotoxins to immobilize fish rapidly: neuromuscular block, and excitotoxic shock. The latter requires the newly characterized peptide %%%kappa%%%-%%%conotoxin%%% PVIIA, which inhibits the Shaker potassium channel, and delta-conotoxin PVIA, which delays sodium-channel inactivation. Despite the extreme biochemical diversity in venoms, the number of effective strategic alternatives for prey capture are limited. How securely prey is initially tethered may strongly influence the venom strategy evolved by a predator.

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13/7/1
DIALOG(R)File 5:Biosis Previews(R)

0015992020 BIOSIS NO.: 200600337415
Effects of ischemia-%%%reperfusion%%% on goat cerebrovascular response to ADP
AUTHOR: Sanchez Ana (Reprint); Salcedo Adeli; Fernandez Nuria; Monge Luis; Garcia-Villalon Angel Luis; Dieguez Godofredo
AUTHOR ADDRESS: Univ Autonoma Madrid, Dept Fisiol, Madrid 28029, Spain** Spain
JOURNAL: FASEB Journal 20 (5, Part 2): pA1157 MAR 7 2006 2006
CONFERENCE/MEETING: Experimental Biology 2006 Meeting San Francisco, CA, USA April 01 -05, 2006; 20060401
SPONSOR: Amer Assoc Anatomists
Amer Physiol Soc
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Amer Soc Nutr
Amer Soc Pharmacol & Expt Therapeut
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: Brain ischemia-%%%reperfusion%%% (I-R) may produce cerebrovascular endothelial dysfunction, and ADP produces endothelial-dependent cerebral vasodilatation. To analyze the effects of I-R on the cerebrovascular response to ADP, 60 min occlusion followed by 60 min %%%reperfusion%%% of the left middle cerebral artery (MCA) was performed in anesthetized goats. Left MCA flow was electromagnetically measured, and resting cerebrovascular resistance after I-R was decreased by 20% (P<0.01). In control conditions, local, intraarterial injections of ADP (0.03-0.3 mu g) and sodium nitroprusside (SNP, 0.3-3 mu g) decreased cerebrovascular resistance, and after I-R ADP increased this resistance whereas the effects of SNP were not altered. Then, the animals were killed and 3 mm-long rings from branches of the left (I-R) and right (control) MCA were prepared for isometric tension recording. Arterial segments precontrated with U46619 (3x 10(-7)-10(-6) M) showed concentration-dependent relaxations to ADP (10(-8)-10(-5) M) and SNP (10(-8)-10(-4) M), and the relaxations to ADP but not to SNP were lower in I-R arteries. The relaxations to ADP but not to SNP were inhibited by L-NAME (10(-4) M) only in control arteries, and the effects of ADP were inhibited by %%%charybdotoxin%%% (10(-7) M) plus apamine (10(-6) M) only in control arteries. Therefore, I-R may produce cerebral vasodilatation with decreased vasodilator reserve and inversion of the cerebrovascular effects of ADP. This altered effects of ADP may be related to endothelial dysfunction with decreased availability of NO and function of K-Ca channels.

13/7/2
DIALOG(R)File 5:Biosis Previews(R)

0015225412 BIOSIS NO.: 200500132049
Opening of Ca2+-activated K+ channels is involved in ischemic preconditioning in canine hearts
AUTHOR: Shintani Yasunori; Node Koichi; Asanuma Hiroshi; Sanada Shoji; Takashima Seiji; Asano Yoshihiro; Liao Win; Fujita Masashi; Hirata Akio; Shinozaki Yoshiro; Fukushima Tom; Nagamachi Yoko; Okuda Hiroko; Kim Jiyoong; Tomoike Hitonobu; Hori Masatsugu; Kitakaze Masafumi (Reprint)
AUTHOR ADDRESS: Cardiol Div Med, Natl Cardiovasc Ctr, 5-7-1 Fujishirodai, Suita, Osaka, 5658565, Japan**Japan
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JOURNAL: Journal of Molecular and Cellular Cardiology 37 (6): p1213-1218 December 2004 2004
MEDIUM: print
ISSN: 0022-2828 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Brief periods of ischemia that precede sustained ischemia can markedly reduce infarct size (IS). a phenomenon that is known its ischemic preconditioning (IP). Several investigators have shown that elevation of the intracellular Ca2+ level (Ca2+i) during the antecedent brief periods of ischemia triggers the cardioprotective mechanism of IP. Since opening of Ca2+ activated K+ (KCa) channels is reported to be cardioprotective, we hypothesized that these channels may be involved in the cardioprotective mechanism of IP. In anesthetized open-chest dogs, myocardial ischemia/%%%reperfusion%%% injury was created by occlusion of the left anterior descending coronary artery (LAD) for 90 min channel opener, reduced IS (IS in NS1619 group and followed by 6 h of %%%reperfusion%%%. First. we showed that the treatment with NS1619, a KCa control group, 19.8 +/- 5.5% vs. 45.4 +/- 3.5% of the area at risk, P < 0.05). Next, four Cycles coronary occulsion for 5 min and %%%reperfusion%%% (IP) were performed before the 90-min occlusion With Or Without the infusion of potent KCa channel inhibitors, iberiotoxin (IbTX) and %%%charybdotoxin%%% (ChTX). IP markedly reduced IS (IS in the IP group was 8.2 +/- 1.8% P < 0.01 VS. control group). Infusion of either of K,,,, channel blockers during IP blunted the IS-limiting effect of IP (IS in the IP + IbTX and IP + ChTX groups was 30.7 +/- 7.0% and 35.5 +/- 3.7% respectively, P < 0.05. vs. IP group). However, the cardioprotective effect MAP wits not blunted by the treatment with chTX when treated only during %%%reperfusion%%% (14.0 +/- 4.1%). Thus, we conclude that the opening of KCa channel is involved in early trigger phase of the molecular mechanism of IP.

13/7/3
DIALOG(R)File 5:Biosis Previews(R)

0014414391 BIOSIS NO.: 200300373110
Eicosapentaenoic acid reduces myocardial injury induced by ischemia and %%%reperfusion%%% in rabbit hearts.
AUTHOR: Ogita Hisakazu; Node Koichi (Reprint); Asanuma Hiroshi; Sanada Shoji; Takashima Seiji; Minamino Tetsuo; Soma Masaaki; Kim Jiyoong; Hori Masatsugu; Kitakaze Masafumi
AUTHOR ADDRESS: Cardiovascular Division, Department of Medicine, Saga

Medical School, 5-1-1 Nabeshima, Saga, 849-8501, Japan**Japan
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JOURNAL: Journal of Cardiovascular Pharmacology 41 (6): p964-969 June 2003
2003
MEDIUM: print
ISSN: 0160-2446
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Intake of fish oil is known to have cardioprotective effects and reduce cardiovascular mortality. However, it is not widely recognized that eicosapentaenoic acid (EPA), one of the n-3 polyunsaturated fatty acids (PUFAs), exerts beneficial effects against myocardial ischemia/%%%reperfusion%%% injury. The purpose of this study is to investigate whether EPA attenuates the severity of myocardial ischemia/%%%reperfusion%%% injury and which cellular mechanism is involved. Rabbits were treated with or without EPA (600 mg/kg/day) for 2 weeks. Infarct size was measured in open-chest rabbits after 30-minute occlusion of the left anterior descending coronary artery (LAD) and after the subsequent 3-hour %%%reperfusion%%%. In several groups, NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide (NO) synthase, or %%%charybdotoxin%%%, a blocker of calcium-activated potassium (KCa) channels, was infused intravenously beginning 20 minutes before LAD occlusion and continuing during %%%reperfusion%%%. Infarct size was reduced in the group treated with EPA compared with the control group (7.2+-1.0% vs 24.6+-2.3%; P<0.01). The occurrence of ventricular arrhythmias in the %%%reperfusion%%% period tended to decrease in the EPA group. Either L-NAME or %%%charybdotoxin%%% partially blunted or completely abolished the infarct size-limiting effect of EPA, respectively. Eicosapentaenoic acid significantly increased the n-3:n-6 ratio of PUFA. Eicosapentaenoic acid reduces myocardial infarct size, mainly via the opening of KCa channel-mediated and partially NO-mediated mechanisms in rabbit hearts.

13/7/4
DIALOG(R)File 5:Biosis Previews(R)

0014141895 BIOSIS NO.: 200300100614
Effect of Propofol on the Membrane Potential Changes Induced by Superoxide and Hydrogen Peroxide in Smooth Muscle Cells of the Rabbit Mesenteric Resistance Artery.
AUTHOR: Hattori Tomonori (Reprint); Imura Nami (Reprint); Katsuya Hirotada (Reprint); Itoh Takeo (Reprint)
AUTHOR ADDRESS: Anesthesiology and Resuscitology, Nagoya-City University, Nagoya, Aichi, Japan**Japan
JOURNAL: Anesthesiology Abstracts of Scientific Papers Annual Meeting (2001): pAbstract No. A-65 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 2001 Annual Meeting of the American Society of Anesthesiologists New Orleans, LA, USA October 13-17, 2001; 20011013
SPONSOR: American Society of Anesthesiologists Inc.
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction Under some pathophysiological conditions (such as ischemic-%%%reperfusion%%% injury), superoxide (O2-) plays an essential role for causing severe tissue damage. It is known that O2- produces a variety of actions in many cells, depending on the cell types. However, the actions of O2- on resistance arteries have not yet been clarified. Propofol, a widely used intravenous anesthetic and sedative agent, has been found to possess antioxidant properties, although this beneficial role of propofol has not been clarified in resistance vessels under physiological conditions. It has been established that the membrane potential plays a significant role on excitation-contraction coupling in smooth muscle cells (SMCs) of the resistance arteries. In our present study, we first investigated the action of O2- on membrane potential in SMCs of rabbit mesenteric resistance arteries (RMA). We also investigated if propofol modified the action of O2- and hydrogen peroxide (H2O2) on membrane potential in SMCs of RMA. Methods Using a microelectrode technique, membrane potential changes were recorded in SMC of endothelium-intact or denuded RMA. The effect of propofol on membrane potential changes was then studied in the presence of O2- or H2O2. The effect of superoxide dismutase (SOD) or catalase was examined as its pre-treatment (and present thereafter). O2- was generated enzymatically by hypoxanthine (0.1mM)/xanthine oxidase (1mU/ml) (HX/XO) reaction. Results HX/XO hyperpolarized the membrane in both endothelium-intact and -denueded strips. SOD did not inhibit (rather enhanced), but catalase inhibited the O2--induced membrane hyperpolarization. In endothelium-intact strips, neither NG-nitro-L-arginine (an inhibitor of NO synthase) nor %%%charybdotoxin%%% (an inhibitor of large and intermediate conductance KCa channels)+apamin (an inhibitor of small conductance KCa channels) modified the O2--induced hyperpolarization. Both diclofenac (an inhibitor of cyclooxygenase) and glibenclamide (an inhibitor of KATP channels) significantly attenuated the O2--induced hyperpolarization. Propofol significantly attenuated the membrane hyperpolarization induced by HX/XO, but not by H2O2. Conclusion These results suggest that in SMC of RMA, O2- is metabolized to H2O2 by endogenous SOD and then H2O2 produces a membrane hyperpolarization . It is also suggested that H2O2 directly acts on SMCs and increases the synthesis of prostaglandins that contribute to an activation of glibenclamide-sensitive KATP channels, thus causing a membrane hyperpolarization. Propofol inhibits the hyperpolarization induced by O2-, but not by H2O2, suggesting that this agent inhibits the O2--induced response via its scavenging action to this active oxygen. This action of propofol may be beneficial to prevent superoxide-induced tissue damage during surgeries.

13/7/5
DIALOG(R)File 5:Biosis Previews(R)

0013923162 BIOSIS NO.: 200200516673
Amelioration of ischemia- and %%%reperfusion%%%-induced myocardial injury by the selective estrogen receptor modulator, raloxifene, in the canine heart
AUTHOR: Ogita Hisakazu; Node Koichi (Reprint); Asanuma Hiroshi; Sanada Shoji; Liao Yulin; Takashima Seiji; Asakura Masanori; Mori Hidezo; Shinozaki Yoshiro; Hori Masatsugu; Kitakaze Masafumi
AUTHOR ADDRESS: Department of Internal Medicine and Therapeutics, Graduate

School of Medicine, Osaka University, 2-2 Yamada-oka, Suita, Osaka, 565-0871, Japan**Japan
JOURNAL: Journal of the American College of Cardiology 40 (5): p998-1005 September 4, 2002 2002
MEDIUM: print
ISSN: 0735-1097
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: OBJECTIVES: We sought to investigate whether raloxifene reduces ischemia-%%%reperfusion%%% injury and what mechanisms are involved in the cardioprotective effects. BACKGROUND: Estradiol-17-beta reduces myocardial infarct size in ischemia-%%%reperfusion%%% injury. Raloxifene, a selective estrogen receptor modulator, demonstrates immediate coronary artery vasorelaxing effects. METHODS: The myocardial ischemia-%%%reperfusion%%% model included anesthetized open-chest dogs after 90-min occlusion of the left anterior descending coronary artery (LAD) and subsequent 6-h %%%reperfusion%%%. Raloxifene and/or other drugs were infused into the LAD from 10 min before coronary occlusion to 1 h after %%%reperfusion%%% without an occlusion period. RESULTS: Infarct size was reduced in the raloxifene (5 mug/kg per min) group compared with the control group (7.2+-2.5% vs. 40.9+-3.9% of the area at risk, p<0.01). Either NG-nitro-L-arginine methyl ester (L-NAME), the inhibitor of nitric oxide (NO) synthase, or %%%charybdotoxin%%%, the blocker of Ca2+-activated K+ (KCa) channels, partially attenuated the infarct size-limiting effect, and both of them completely abolished the effect. The incidence of ventricular fibrillation was also less in the raloxifene group than in the control group (11% vs. 44%, p<0.05). Activity of p38 mitogen-activated protein (MAP) kinase increased with 15-min ischemia, and raloxifene pretreatment inhibited the activity. Myeloperoxidase activity of the 6-h reperfused myocardium was also attenuated by raloxifene. CONCLUSIONS: These data demonstrate that raloxifene reduces myocardial ischemia-%%%reperfusion%%% injury by mechanisms dependent on NO and the opening of KCa channels in canine hearts. Deactivation of p38 MAP kinase and myeloperoxidase by raloxifene may be involved in the cellular mechanisms of cardioprotection.

13/7/6
DIALOG(R)File 5:Biosis Previews(R)

0013760898 BIOSIS NO.: 200200354409
Protease-activated receptor (PAR)-2 activation causes EDHF-like coronary vasodilation: Selective preservation in ischemia-%%%reperfusion%%% injury, involvement of lipoxygenase products, VR1 receptors and C-fibers
AUTHOR: McLean Peter (Reprint); Ahluwalia Amrita
AUTHOR ADDRESS: Centre for Clinical Pharmacology, William Harvey Research Institute, Charterhouse Square, London, ECIM 6BQ, UK**UK
JOURNAL: FASEB Journal 16 (4): pA569 March 20, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002; 20020420
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We investigated the effects of PAR2 activation on coronary tone in isolated perfused rat hearts and elucidated the underlying mechanisms of any observed effects. Whilst having a negligible effect on ventricular contractility, the PAR2 activating peptide, SLIGRL and trypsin produced an dose-dependent coronary vasodilatation. Following I/R injury the dilator response to acetylcholine was converted to constriction, while the response to SLIGRL was selectively preserved. Removal of the endothelium but not treatment with L-NAME (300muM), indomethacin (5muM) or oxyhemoglobin (10muM) inhibited the response to SLIGRL and trypsin. Treatment with the K+channel blockers TEA (10mM), %%%charybdotoxin%%% (20nM)/apamin (100nM) or elevated potassium (20mM) significantly suppressed responses. Similarly, inhibition of lipoxygenase with nordihydroguaiaretic acid (1muM), desensitization of C-fibers using capsaicin (1muM, 20 min) or blockade of vanilloid (VR1) receptors using capsazepine (3muM) inhibited SLIGRL and trypsin-induced coronary vasodilation. This study shows, for the first time, that PAR2 activation causes endothelium-dependent coronary vasodilation that is preserved following I/R injury and is not mediated by NO or prostanoids, but involves the release of an endothelium-derived hyperpolarizing factor (EDHF), possibly a lipoxygenase-derived eicosanoid, and activation of VR1 receptors on sensory C-fibers.

13/7/7
DIALOG(R)File 5:Biosis Previews(R)

0013670246 BIOSIS NO.: 200200263757
The selective estrogen receptor modulator, raloxifene, reduces infarct size and ventricular arrhythmias in canine hearts
AUTHOR: Ogita Hisakazu (Reprint); Kitakaze Masafumi (Reprint); Node Koichi (Reprint); Asanuma Hiroshi (Reprint); Sanada Shoji (Reprint); Liao Yulin (Reprint); Takashima Seiji (Reprint); Asakura Masanori (Reprint); Mori Hidezo; Shinozaki Yoshiro; Hori Masatsugu
AUTHOR ADDRESS: Graduate Sch of Med, Osaka Univ, Osaka, Japan**Japan
JOURNAL: Circulation 104 (17 Supplement): pII.150 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/8
DIALOG(R)File 5:Biosis Previews(R)

0013669909 BIOSIS NO.: 200200263420
Mitochondrial Ca2+-activated K+ channels are a major component of K+ uniport activity in mitochondria of cardiac myocytes
AUTHOR: Xu Wenhong (Reprint); O'Rourke Brian (Reprint)

AUTHOR ADDRESS: Johns Hopkins Univ, Baltimore, MD, USA**USA
JOURNAL: Circulation 104 (17 Supplement): pII.80 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/9
DIALOG(R)File 5:Biosis Previews(R)

0013627845 BIOSIS NO.: 200200221356
Protease-activated receptor-2 activation causes EDHF-like coronary vasodilation: Selective preservation in ischemia/%%%reperfusion%%% injury: Involvement of lipoxygenase products, VR1 receptors, and C-fibers
AUTHOR: McLean Peter G (Reprint); Aston Daniel; Sarkar David; Ahluwalia Amrita
AUTHOR ADDRESS: Centre for Clinical Pharmacology, William Harvey Research Institute, London, EC1M 6BQ, UK**UK
JOURNAL: Circulation Research 90 (4): p465-472 March 8, 2002 2002
MEDIUM: print
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activation of protease-activated receptor (PAR)-2 has been proposed to be protective in myocardial ischemia/%%%reperfusion%%% (I/R) injury, an effect possibly related to an action on the coronary vasculature. Therefore, we investigated the effects of PAR2 activation on coronary tone in isolated perfused rat hearts and elucidated the mechanisms of any observed effects. Although having a negligible effect on ventricular contractility, the PAR2 activating peptide SLIGRL produced an endothelium-dependent coronary vasodilation (ED50=3.5 nmol). Following I/R injury, the response to SLIGRL was selectively preserved, whereas the dilator response to acetylcholine was converted to constriction. Trypsin also produced a vasodilator dose-response curve that was biphasic in nature (ED50-1=0.36 U, ED50-2=38.71 U). Desensitization of PAR2 receptors indicated that the high potency phase was mediated by PAR2. Removal of the endothelium but not treatment with L-NAME (300 mumol/L), indomethacin (5 mumol/L), or oxyhemoglobin (10 mumol/L) inhibited the response to SLIGRL and trypsin. Treatment with the K+-channel blockers TEA (10 mmol/L), %%%charybdotoxin%%% (20 nmol/L)/apamin (100 nmol/L), or elevated potassium (20 mmol/L) significantly suppressed responses. Similarly, inhibition of lipoxygenase with nordihydroguaiaretic acid (1 mumol/L), eicosatetraynoic acid (1 mumol/L), or baicalein (10 mumol/L), desensitization of C-fibers using capsaicin (1 mumol/L, 20 minutes), or blockade of vanilloid (VR1) receptors using capsazepine (3 mumol/L) inhibited the responses. This study shows, for the first time, that PAR2 activation causes endothelium-dependent coronary vasodilation that is preserved after I/R injury and is not mediated by NO or prostanoids, but involves the release of an endothelium-derived hyperpolarizing factor

(EDHF), possibly a lipoxygenase-derived eicosanoid, and activation of VR1 receptors on sensory C-fibers.

13/7/10
DIALOG(R)File 5:Biosis Previews(R)

0013022396 BIOSIS NO.: 200100194235
Amelioration of ischemia- and %%%reperfusion%%%-induced myocardial injury by raloxifene: Roles of nitric oxide and the opening of calcium-activated potassium channels
AUTHOR: Ogita Hisakazu (Reprint); Kitakaze Masafumi (Reprint); Node Koichi (Reprint); Asanuma Hiroshi (Reprint); Sanada Shoji (Reprint); Takashima Seiji (Reprint); Asakura Masanori (Reprint); Liao Yulin (Reprint); Shinozaki Yoshiro (Reprint); Mori Hidezo (Reprint); Kuzuya Tsunehiko (Reprint); Hori Masatsugu (Reprint)
AUTHOR ADDRESS: Osaka University Graduate School of Medicine, Suita, Japan **Japan
JOURNAL: Journal of the American College of Cardiology 37 (2 Supplement A): p362A-363A February, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 50th Annual Scientific Session of the American College of Cardiology Orlando, Florida, USA March 18-21, 2001; 20010318
SPONSOR: American College of Cardiology
ISSN: 0735-1097
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/11
DIALOG(R)File 5:Biosis Previews(R)

0011805842 BIOSIS NO.: 199900065502
Potentiated EDHF mediated dilations in the rat middle cerebral artery following ischemia/%%%reperfusion%%%
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AUTHOR ADDRESS: Dep. Anesthesiol., Baylor Coll. Med., Houston, TX 77030, USA**USA
JOURNAL: Society for Neuroscience Abstracts 24 (1-2): p1169 1998 1998
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0008165592 BIOSIS NO.: 199293008483
EFFECT OF POTASSIUM CHANNEL BLOCKADE ON THE ANTI-ISCHEMIC ACTIONS OF MECHANISTICALLY DIVERSE AGENTS
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JOURNAL: Journal of Pharmacology and Experimental Therapeutics 259 (1): p 97-103 1991
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LANGUAGE: ENGLISH

ABSTRACT: The ATP-sensitive potassium channel opener, cromakalim, protects ischemic hearts and its effective can be reversed by glyburide. It is presently unknown if glyburide can abolish the anti-ischemic effects of mechanistically different agents or if blockers of other potassium channels can abolish the protective effects of cromakalim. Thus, the effect of glyburide on previously reported cardioprotective agents was tested in globally ischemic/reperfused isolated rats hearts. Calcium antagonists, sodium channel blockers and calmodulin antagonists were found to significantly improve postischemic contractile function and reduce lactate-dehydrogenase release after 25 min of global ischemia and 30 min of %%%reperfusion%%%. Glyburide did not reverse their cardioprotective effects. 5-(N,N-dimethyl)amiloride, an inhibitor of Na+/H+ exchange, significantly reduced lactatedehydrogenase release without improving postischemic contractile function, and glyburide did not reverse this. The potassium channel opener, cromakalim, protected ischemic rat hearts (improved recovery of contractile function and reduced enzyme release) and this was abolished by glyburide. %%%Charybdotoxin%%% blocks both calcium-activated potassium channels and E-4031 the delayed rectifier potassium channels. Neither was found to effect the action of the potassium channel opener, cromakalin. These data indicate that glyburide is selective in that it only blocks the anti-ischemic efects of potassium channel openers and not other cardioprotective compounds. In addition, cromakalim is unaffected by blockers of other potassium channels, further indicating selectivity of glyburide for ATP-sensitive potassium channels.

? t s17/7/1

17/7/1
DIALOG(R)File 5:Biosis Previews(R)

0013219304 BIOSIS NO.: 200100391143
Autoradiographic localization of N-type VGCCs in gerbil hippocampus and failure of omega-%%%conotoxin%%% MVIIA to attenuate neuronal injury after transient cerebral %%%ischemia%%%
AUTHOR: Azimi-Zonooz Aryan (Reprint); Kawa Chad B; Dowell Cheryl D; %%%Olivera Baldomero M%%%
AUTHOR ADDRESS: Department of Pediatrics, Oregon Health Sciences University, Portland, OR, 97201, USA**USA
JOURNAL: Brain Research 907 (1-2): p61-70 13 July, 2001 2001

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LANGUAGE: English

ABSTRACT: In the mammalian central nervous system, transient global %%%ischemia%%% of specific duration causes selective degeneration of CA1 pyramidal neurons in hippocampus. Many of the %%%ischemia%%%-induced pathophysiologic cascades that destroy the neurons are triggered by pre- and postsynaptic calcium entry. Consistent with this, many calcium channel blockers have been shown to be neuroprotective in global models of %%%ischemia%%%. omega-%%%Conotoxin%%% MVIIA, a selective N-type VGCC blocker isolated from the venom of Conus magus, protects CA1 neurons in the rat model of global %%%ischemia%%%, albeit transiently. The mechanism by which this peptide renders neuroprotection is unknown. We performed high-resolution receptor autoradiography with the radiolabeled peptide and observed highest binding in stratum lucidum of CA3 subfield, known to contain inhibitory neurons potentially important in the pathogenesis of delayed neuronal death. This finding suggested that the survival of stratum lucidum inhibitory neurons might be the primary event, leading to CA1 neuroprotection after %%%ischemia%%%. Testing of this hypothesis required the reproduction of its neuroprotective effects in the gerbil model of global %%%ischemia%%%. Surprisingly, we found that omega-MVIIA did not attenuate CA1 hippocampal injury after 5 min of cerebral %%%ischemia%%% in gerbil. Possible reasons are discussed. Lastly, we show that the peptide can be used as a synaptic marker in assessing short and long-term changes that occur in hippocampus after %%%ischemic%%% injury.

? t s18/7/1-2

18/7/1
DIALOG(R)File 5:Biosis Previews(R)

0012127173 BIOSIS NO.: 199900386833
The block of Shaker K+ channels by kappa-conotoxin PVIIA is state dependent
AUTHOR: Terlau Heinrich; Boccaccio Anna; %%%Olivera Baldomero M%%%; Conti Franco (Reprint)
AUTHOR ADDRESS: Istituto di Cibernetica e Biofisica, CNR, 16149, Genova, Italy**Italy
JOURNAL: Journal of General Physiology 114 (1): p125-140 July, 1999 1999
MEDIUM: print
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LANGUAGE: English

ABSTRACT: kappa-conotoxin PVIIA is the first conotoxin known to interact with voltage-gated potassium channels by inhibiting Shaker-mediated currents. We studied the mechanism of inhibition and concluded that PVIIA blocks the ion pore with a 1:1 stoichiometry and that binding to open or closed channels is very different. Open-channel properties are revealed by relaxations of partial block during step depolarizations, whereas double-pulse protocols characterize the slower reequilibration of closed-channel binding. In 2.5 mM-(K+)o, the IC50 rises from a tonic

value of apprx50 to apprx200 nM during openings at 0 mV, and it increases e-fold for about every 40-mV increase in voltage. The change involves mainly the voltage dependence and a 20-fold increase at 0 mV of the rate of PVIIA dissociation, but also a fivefold increase of the association rate. PVIIA binding to Shaker DELTA6-46 channels lacking N-type inactivation or to wild phenotypes appears similar, but inactivation partially protects the latter from open-channel unblock. Raising (K+)o to 115 mM has little effect on open-channel binding, but increases almost 10-fold the tonic IC50 of PVIIA due to a decrease by the same factor of the toxin rate of association to closed channels. In analogy with %%%charybdotoxin%%% block, we attribute the acceleration of PVIIA dissociation from open channels to the voltage-dependent occupancy by K+ ions of a site at the outer end of the conducting pore. We also argue that the occupancy of this site by external cations antagonizes on binding to closed channels, whereas the apparent competition disappears in open channels if the competing cation can move along the pore. It is concluded that PVIIA can also be a valuable tool for probing the state of ion permeation inside the pore.

18/7/2
DIALOG(R)File 5:Biosis Previews(R)

0011292389 BIOSIS NO.: 199800086636
kappa-Conotoxin PVIIA is a peptide inhibiting the Shaker K+ channel
AUTHOR: Shon Ki-Joon; Stocker Martin; Terlau Heinrich; Stuehmer Walter; Jacobsen Richard; Walker Craig; Grilley Michelle; Watkins Maren; Hillyard David R; Gray William R; %%%Olivera Baldomero M%%% (Reprint)
AUTHOR ADDRESS: Univ. Utah, 201 S. Biology, Salt Lake City, UT 84112, USA** USA
JOURNAL: Journal of Biological Chemistry 273 (1): p33-38 Jan. 2, 1998 1998
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ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: kappa Conotoxin PVIIA (kappa-PVIIA), a 27-amino acid toxin from Conus purpurascens venom that inhibits the Shaker potassium channel, was chemically synthesized in a biologically active form. The disulfide connectivity of the peptide was determined. A structure was give for kappa-Conotoxin PVIIA. This is the first Conus peptide known to target K+ channels. Although the Shaker K+ channel is sensitive to kappa-PVIIA, the rat brain Kv1.1 subtype is resistant. Chimeras between Shaker and the Kv1.1 K+ channels were constructed and expressed in Xenopus oocytes. Only channels containing the putative pore-forming region between the fifth and sixth transmembrane domains of Shaker retained toxin sensitivity, indicating that the toxin target site is in this region of the channel. Evidence is presented that kappa-PVIIA interacts with the external tetraethyl-ammonium binding site on the Shaker channel. Although both kappa-PVIIA and %%%charybdotoxin%%% inhibit the Shaker channel, they must interact differently. The F425G Shaker mutation increases %%%charybdotoxin%%% affinity by 3 orders of magnitude but abolishes kappa-PVIIA sensitivity. The precursor sequence of kappa-PVIIA was deduced from a cDNA clone, revealing a prepropeptide comprising 72 amino acids. The N-terminal region of the K-PVIIA prepropeptide exhibits

striking homology to the omega, muO-, and delta-conotoxins. Thus, at least four pharmacologically distinct superfamilies of Conus peptides belong to the same "O" superfamily, with the omega and KAPPA-conotoxins forming one branch, and the delta and muO-conotoxins forming a second major branch.

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